



The atrial fibrillation burden during the blanking period is predictive of time to recurrence after catheter ablation

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ABSTRACT

Objective: This study aimed to assess whether atrial fibrillation (AF) occurrence or its corresponding daily mean burden (in minutes/day) during the mid to late blanking period after pulmonary vein isolation (PVI), predicts AF recurrence.

Methods: Analysis of consecutive first PVI ablation patients undergoing prolonged electrocardiogram (ECG) monitoring during the second and third months after PVI. The clinical variables, total AF burden, and their relationship with time to recurrence were studied.

Results: 477 patients with a mean age of 56.9 (SD = 12.3) years (63.7 % male; 71.7 % paroxysmal AF), from which 317 (66.5 %) had an external event recorder between 30 and 90 days after ablation. Median follow-up of 16.0 (P 25:12.0; P 75:33.0) months, 177 (37 %) patients had an AF recurrence, with 106 (22.2 %) having the first episode after 12 months of follow-up. In the group of patients with an event recorder, 80 (25.2 %) had AF documented during the blanking period. Multivariable analysis showed that AF during the blanking period was associated with a 4-fold higher risk of recurrence (HR: 3.98; 95 %CI: 2.95–5.37), and, compared to patients in sinus rhythm, those with an AF burden ≥ 23 min/day had an approximately 7-fold higher risk of recurrence (HR estimate: 6.79; 95 %CI: 4.56–10.10).

Conclusions: The probability of experiencing AF recurrence can be predicted by atrial tachyarrhythmia episodes during the second and third months after PVI. Atrial arrhythmias burden > 23 min/day has a high predictive ability for recurrence.

1. Background

Atrial fibrillation (AF) is the most common sustained arrhythmia and is associated with a substantial economic burden and significant morbidity and mortality [1,2]. In the past two decades, the knowledge of AF pathophysiology has led to significant developments in the treatment options, particularly regarding catheter ablation [3,4,5]. Ablation, based on pulmonary vein isolation (PVI), represents an essential

rhythm-control strategy for the management of paroxysmal, drug-refractory AF, being one of the most common cardiac ablation procedures performed worldwide.

A fundamental aspect after PVI is the assessment of arrhythmic recurrence. AF can occur in the first weeks to months after PVI or even after a long-term period free of AF [6]. The first three months after PVI is known as the blanking period, and atrial tachyarrhythmias (AT/AF) during it is considered a transitory phenomenon without clinical

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significance in predicting late AF recurrence. However, in recent years, the clinical implication of the occurrence of AT/AF in this period has come to be valued.

The incidence of AT/AF is highest in the immediate post-ablation period and progressively decreases after that [7,8]. Since the observation by Oral et al. in 2002 [9], different studies have consistently found that early recurrence of AT/AF occurs mainly during the first two weeks after PVI [10,11]. This means that AT/AF as a predictor of late recurrences probably became more significant after the first month [12]. Therefore, we conducted this study to investigate the incidence of AT/AF during the early period after PVI by using an external event loop recorder and its relationship with recurrence rate and time to AF occurrence during follow-up.

2. Methods

2.1. Study population

We studied 477 consecutive patients with symptomatic drug-refractory paroxysmal (PAF) or persistent (PsAF) AF who received an index AF catheter ablation between 05/2005 and 02/2020 in the Centro Hospitalar de Lisboa Central. Subject data were excluded from the current analysis if patients were diagnosed with long-standing persistent AF (continuous AF > 12 months), had incomplete baseline data reported, or were redo procedures. AF was classified as PAF if arrhythmia episodes terminated spontaneously, or with intervention within seven days of onset, or as PsAF if the episodes were sustained, lasted longer than seven days, but <12 months [1].

The hospital ethics committee approved the study protocol (Ethics Committee approval number 974/2020). All participants provided written informed consent for data collection, and the study was conducted according to the Declaration of Helsinki guidelines.

2.2. Ablation procedure

Every patient underwent a routine preprocedural transthoracic echocardiogram to evaluate left ventricular ejection fraction left atrial dimensions, screen for structural heart disease, and computed tomography or magnetic resonance imaging (with the segmentation of the left atrium) to assess left atrial anatomy and to exclude the presence of intracardiac thrombi. Additionally, if the mentioned imaging study was performed > 48 h before ablation, transesophageal echocardiography was done on the day of the procedure (for exclusion of thrombi). Patients underwent ablation after continued oral anticoagulation (for at least four weeks before ablation) using warfarin with a therapeutic INR (2.0–3.0) or direct oral anticoagulants (DOAC), with one dosage omitted in the evening before the ablation. Continuous monitoring of oxygen saturation and ECG were maintained throughout the ablation. All procedures were carried out under conscious sedation or general anesthesia.

In brief, the protocol steps for radiofrequency catheter ablation (RFCA) in the researchers' institution consisted in: 1. positioning a decapolar catheter through the right femoral vein to guide the transseptal puncture and to pace the left atrium, 2. A transseptal puncture by fluoroscopic guidance 3. three-dimensional mapping of the left atrium performed with either the EnSite NavX/Velocity (Abbott Laboratories, Abbott Park, IL) or CARTO (Biosense Webster, Irvine, California) system. Radiofrequency applications were performed using an open-irrigated-tip catheter (FlexAbility™, Abbott or ThermoCool Smart-Touch® SurroundFlow, Biosense Webster) with point-by-point-lesions. When using the cryoenergy, the ablation balloon system used was the Arctic Front™ (Medtronic, Inc., Minneapolis, MN, USA) with the 28-mm balloon. Different cryoballoon positions were assessed (by injecting contrast into the vein distal to the balloon) to ensure optimal occlusion. Regarding energy applications, after successful PVI (240 s, aiming for a minimum temperature of less than – 40 °C), an additional freeze-cycle

of the same duration was applied at the operator's discretion. The phrenic nerve function was checked during energy application in the right pulmonary veins [13].

2.3. Post ablation evaluation

AF recurrence-free survival was the primary endpoint, considering an AF recurrence as any post-90-day blanking atrial tachyarrhythmias lasting 30 s or longer, sustained symptomatic episodes of rapid palpitations, prescription of antiarrhythmic drugs (class I or III), or repeat ablation.

After the ablation procedure, patients were discharged on antiarrhythmic drugs (AAD) at the operator's discretion, together with oral anticoagulation. Patients were observed for routine follow-up in the outpatient clinic 1–3 months after the procedure and every six months (or earlier, if symptoms) during the first two years post-ablation. At each visit, a standard 12-lead ECG was obtained. Patients were monitored with an external loop recorder (Spiderflash™ and Eventscope™ 3 analysis software, MicroPort CRM, Clamart, France) between 30 and 90 days after AF ablation. After the blanking period, patients were followed-up with a 24-hour-Holter at each outpatient visit.

AAD was continued for six months after the ablation procedure and was withdrawn - except for beta-blockers - if the patients were free from arrhythmia-related symptoms. Oral anticoagulation was re-evaluated in the third month, and the decision to continue was based on the CHA2DS2-VASc score. Clinical events occurring during the follow-up were evaluated.

2.4. Statistical analysis

Results are expressed as mean (\pm standard deviation, SD), median (P25; P75), or as frequencies and percentages, as appropriate. AT/AF burden during the blanking period, corresponding to the mean duration time of AT/AF per day (referred to as AF burden), was obtained by dividing the number of minutes with arrhythmia by the number of days of device use. A time-dependent area under the ROC (Receiver Operating Characteristic) curve was used to study its discriminative ability regarding future recurrence along the follow-up time. The inverse probability of censoring weighting (IPCW) method was applied to estimate these time-dependent areas under the ROC curve. A cut-off point for this AF burden that best predicted AF recurrence was obtained with only those patients with an AF burden different from zero, and a new binary variable was constructed. Martingale residuals, proper to assess the functional form of covariates in the Cox proportional hazards model, were used to identify this point [14]. Time-dependent sensitivity, specificity, and positive and negative predictive values were estimated for this binary AF burden variable.

Two survival analyses to study time until recurrence were performed considering the primary exposures: having had (or not) AF episodes during the blanking period, and corresponding AF burden. Firstly, Kaplan-Meier estimator was used to obtain recurrence-free survival estimates. Log-rank test was further applied to compare AF survival functions between groups. Secondly, univariable and multivariable Cox regression models were fitted to the data, considering the occurrence of AF episodes or AF burden, during the blanking period, as independent variables in two separate multivariable analyses. The association of these two risk factors with recurrence-free survival was adjusted by several covariates, such as age, sex, comorbidities, episodes of arrhythmia pattern, and body mass index, among others. The proportional hazards assumption was checked using formal statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals. Because this assumption was violated for the binary variable corresponding to the number of comorbidities (zero or one vs. ≥ 2), a model with time-varying coefficients was fitted to the data [15].

A level of significance $\alpha = 0.05$ was considered. All data were analyzed using STATA (StataCorp. 2017. Stata Statistical Software:

Release 15. College Station, TX: StataCorp LLC.) and R software (R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>).

3. Results

3.1. Baseline clinical characteristics

This retrospective cohort study considered four hundred and seventy-seven consecutive patients with a median follow-up time of 16.0 (P₂₅:12.0; P₇₅:33.0) months. Cohort's mean age was 56.9 (SD = 12.3), and 36.3 % were women (Table 1). The baseline pattern of AF was paroxysmal in 71.7 % and persistent in 28.3 %. All patients underwent circumferential PVI. RFCA using contact-force technology was used in 295 patients, and ablation using the second-generation cryoballoon in 182 patients. Cavo-tricuspid isthmus ablation was performed in 29 patients with previous documentation of typical atrial flutter.

Detailed baseline clinical and demographic characteristics of the study population are reported in Table 1.

3.2. Atrial fibrillation recurrence

One hundred and seventy-seven (37.1 %) patients had an AF recurrence, from which 106 (59.9 %) occurred after 12 months of follow-up. Recurrence-free survival estimate is depicted in Fig. 1.

Considering the cardiac rhythm recorded during the blanking period (sinus rhythm vs. AF): from patients with sinus rhythm (n = 370), 99 (26.8 %) had an AF recurrence, whereas, in patients with documented AF (n = 107, 22.4 %), 78 (72.9 %) had an AF recurrence. Fig. 2 shows a significant difference in recurrence-free survival between these two groups of patients (p < 0.001).

3.3. Event recorder data analysis

The external event recorder was used by 317 patients during the "late" blanking period after the ablation procedure for a median time of 21 (min = 5, max = 34) days. Regarding AT/AF burden, 237 patients had no AT/AF (zero minutes), and 80 (25.2 %) with AT/AF episode(s) had a median of 29.5 (P₂₅ = 6.9, P₇₅ = 96.2) minutes of arrhythmia burden. The time-dependent discriminative ability of AF burden during the blanking period to distinguish between patients who relapsed from those who did not was characterized by the following time-dependent

Table 1
Population characteristics.

Variables	Number of patients (n = 477)
Paroxysmal AF, n (%)	342 (71.7)
Male sex, n (%)	304 (63.7)
Mean age (SD), years	56.9 (12.3)
Mean LA diameter (SD), mm	43.9 (6.9)
Mean left atrial indexed volume (SD), ml/m ²	38.3 (12.1)
Median CHA ₂ DS ₂ -VASc (P ₂₅ ; P ₇₅)	1.0 (1.0; 2.0)
Mean Body Mass Index (SD), Kg/m ²	28.15 (4.88)
Hypertension, n (%)	281 (58.9)
Hypercholesterolemia, n (%)	135 (28.3)
Diabetes mellitus, n (%)	35 (7.3)
Coronary artery disease, n (%)	25 (5.2)
OSAS, n (%)	52 (10.9)
Heart failure, n (%)	44 (9.2)
Chronic kidney disease, n (%)	5 (1.0)
Previous Stroke/TIA, n (%)	17 (3.6)
Previous pulmonary/peripheral Embolism, n (%)	7 (1.5)
Median follow-up (P ₂₅ ; P ₇₅), months	16.0 (12.0; 33.0)

Legend: AF = atrial fibrillation, LA = left atrium, OSAS = obstructive sleep apnea syndrome, TIA = transient ischemic accident, SD = standard deviation, P₂₅ = 25th percentile, P₇₅ = 75th percentile.

area under the curve of the receiver-operator characteristic to t (time in months) 6 = 85.4 %, t = 9, 78.3 %, t = 12, 71.2 %, t = 24, 68.9 % (see Table 2). A decreasing trend in the area under the ROC curve may be observed.

Using the data corresponding to the 80 patients with an AT/AF burden different from zero, in whom 67.5 % (n = 54) had a recurrence, a cut-off point for this burden (AF mean duration time per day) was determined (Fig. 3).

In this figure, the smooth function should be linear to satisfy the standard Cox proportional hazards model linearity assumption [14]. However, this graphical check shows a nonlinearity and, accordingly, although this covariate could be modeled with a nonlinear function, we proceeded to its discretization for clinical practice use. We considered the cut-off point where the smooth function crosses the reference line (23 min of AF per day), below which the risk of recurrence is lower. At 24 months of follow-up, this variable (AF burden < 23 min vs. AF burden ≥ 23 min) showed a sensitivity of 33.4 %, a specificity of 91.1 %, and positive and negative predictive values of 60.0 % and 77.5 %, respectively (Table 3).

A categorical variable with three categories (no AF burden, with burden < 23 min per day, ≥ 23 min per day) emerged from the former analysis. No AF burden category includes patients with zero minutes of arrhythmia (n = 237) and those that did not use the external event recorder but had no clinical AF episodes (n = 133). The comparison of recurrence-free survival of these three groups of patients is shown in Fig. 4.

3.3.1. Univariable analysis

Results of the univariable analysis for AF recurrence are shown in Table 4. Variables that attained a p-value < 0.25 were selected for the multivariable study.

3.3.2. Multivariable analysis

Regarding the occurrence of AF episode(s) during the blanking period, no multivariable model was achieved, and only this variable remained in the final model. Accordingly, the results are the same as those of the univariable analysis (Table 3) and patients that had AF episodes during the blanking period had approximately a 4-fold higher risk of recurrence (HR: 3.98; 95 %CI: 2.95–5.37); p < 0.001).

Regarding AF burden during the blanking period, results of the multivariable analysis are presented in Table 4. A violation of the proportional hazards assumption was observed for the number of comorbidities during the multivariable modeling process of the data using the Cox regression model (supplementary material Fig. 1).

Multivariable analysis results showed that, compared to patients with sinus rhythm, those with an AF burden ≥ 23 min/day had an approximately 7-fold higher risk of recurrence (HR estimate: 6.79; 95 %CI: 4.56–10.10), while for patients with an AF burden < 23 min/day this risk increase was lower (HR estimate: 2.60; 95 %CI: 1.54–4.47).

Changing the reference category to an AF burden ≥ 23 min/day enabled the comparison of the risk recurrence of patients with an AF burden < 23 min/day with those with a higher burden. Accordingly, patients with a lower AF burden had a 61 % decrease in the risk of recurrence when compared with those with an AF burden ≥ 23 min/day (HR estimate: 0.39; 95 %CI: 0.21–0.70). Regarding the number of comorbidities, having more than one comorbidity increases the risk of recurrence, although this increase was only statistically significant beyond ≈30 months of follow-up after catheter ablation (HR estimate: 3.25; 95 %CI: 1.70–6.23).

4. Discussion

4.1. Main findings

The main findings of the present study are 1) patients with AT/AF episodes lasting > 30 s during the "late" blanking period (between 31

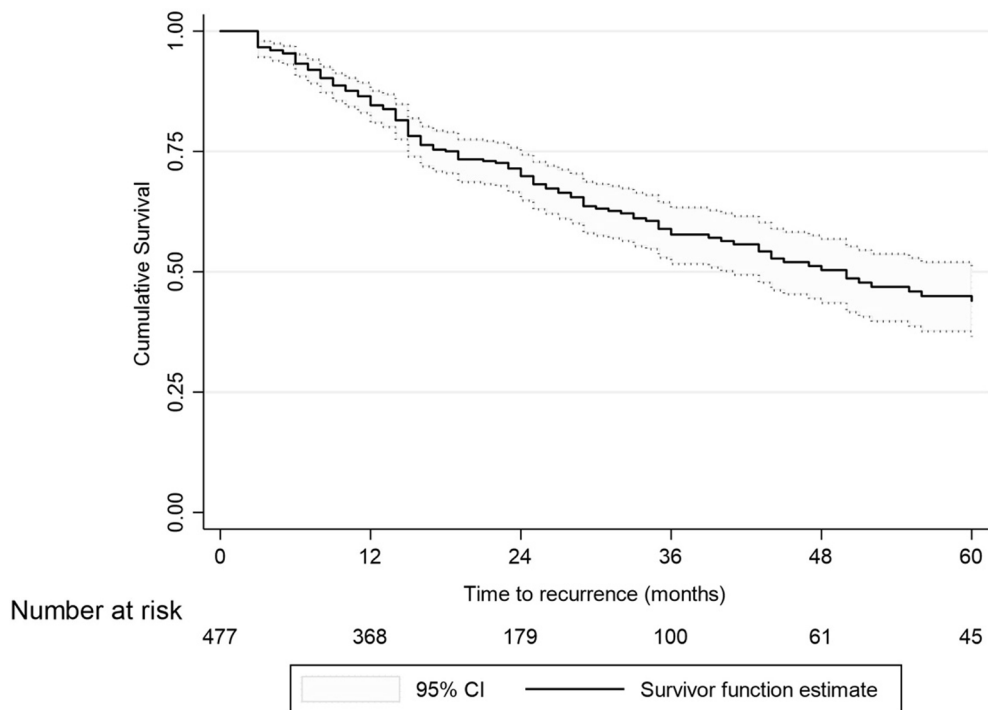


Fig. 1. Kaplan-Meier estimate of recurrence-free survival (estimated median = 47 months; 95 % CI: 38.71–55.29).

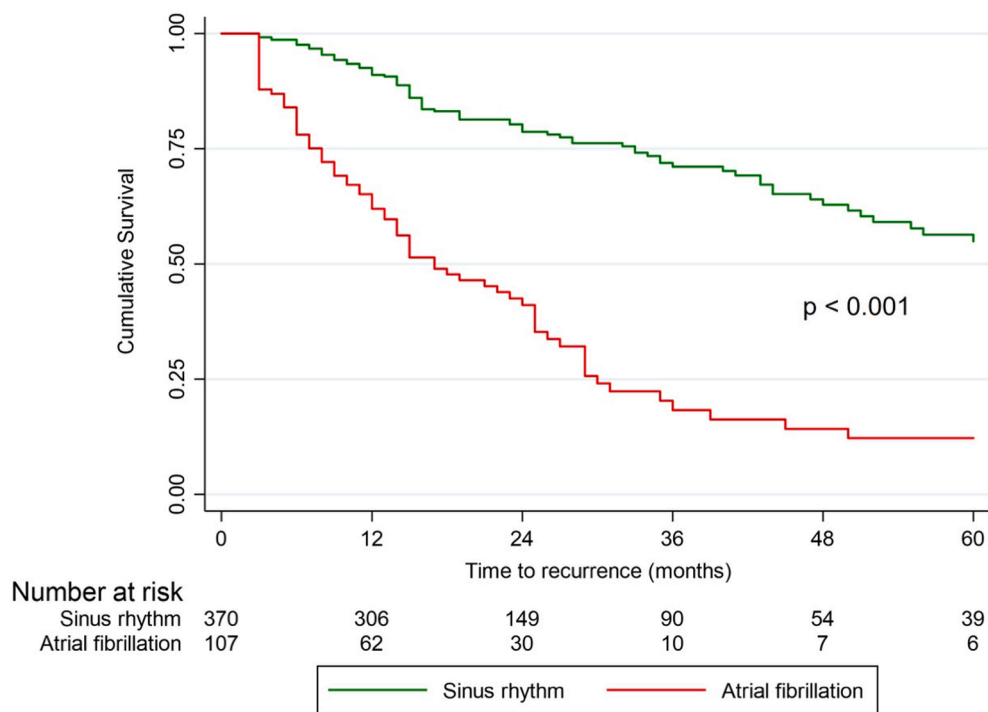


Fig. 2. Kaplan-Meier estimates recurrence-free survival according to cardiac rhythm during the blanking period: sinus rhythm (green line) and atrial fibrillation (red line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and 90 days post-PVI) had a significantly higher risk of long-term AF recurrence than those with sinus rhythm during all blanking period, 2) a total burden of AT/AF above 23 min during the blanking period was correlated with an approximately 7-fold risk of AF recurrence. Also, having more than one comorbidity significantly increases the risk of recurrence beyond 30 months after catheter ablation.

In the early period after AF ablation, the occurrence of AT/AF is a

common finding but may not necessarily imply long-term ablation failure. The first three months after ablation are usually not considered regarding reintervention and procedural success reports [16,17]. Furthermore, it has been accepted that the incidence of early AT/AF episodes is frequent soon after the ablation, decreasing in the following days [18]. Indeed, the number of atrial arrhythmias decreases during the 3-month blinding period [19,20].

Table 2
Performance of binary AF burden during the blanking period as a diagnostic test of AF recurrence.

Time (months)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
t = 6	68.8	88.4	24.3	98.1
t = 9	58.5	89.6	37.0	95.4
t = 12	47.1	88.9	40.6	91.3
t = 24	33.4	91.1	60.0	77.5

Legend: AF-atrial fibrillation; PPV: Positive Predictive value; NPV: Negative Predictive value.

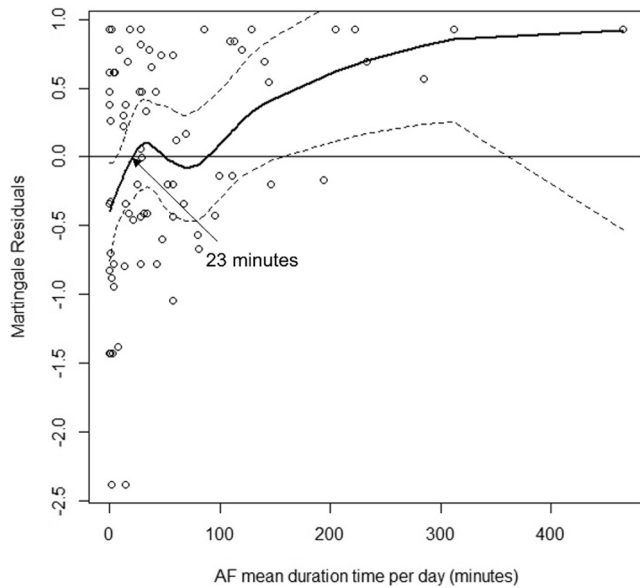


Fig. 3. The plot of martingale residuals versus AF mean duration time per day to assess the functional form of this covariate in the Cox proportional hazards model. The superimposed smooth function in this plot is represented by the solid black line (with a corresponding 95 % confidence interval – dashed lines).

Table 3
Univariable analysis results.

Variables	HR estimate	95 % CI	p-value
Female sex	1.26	0.93–1.70	0.145
Age	1.02	1.01–1.03	0.001
Body Mass Index	1.03	1.01–1.06	0.018
Paroxysmal AF	0.65	0.47–0.89	0.008
Comorbidities (≥2)	1.40	1.04–1.87	0.027
Anatomical variant (yes)	1.33	0.97–1.84	0.082
Average Platelet Volume	1.07	0.94–1.22	0.339
PDW	0.96	0.89–1.04	0.275
Monocytes/HDL ratio*	1.03	1.00–1.06	0.025
Neutrophil/lymphocyte ratio	0.93	0.83–1.05	0.233
Monocyte/lymphocyte ratio**	0.49	0.11–2.13	0.342
CT scan LA	1.04	1.00–1.09	0.047
AF during blanking period	3.98	2.95–5.37	<0.001
AF burden < 23 min/day	2.37	1.39–4.03	0.001
AF burden ≥ 23 min/day	6.54	4.40–9.71	<0.001
AF burden min/day***	1.07	1.05–1.09	<0.001

Legend: AF = atrial fibrillation, PDW = Platelet Distribution Width, HDL = High-density lipoprotein, CT Computed Tomography, LA = left atrium, HR – Hazard Ratio, CI – Confidence Interval; * For each 0.001 unit increase; ** For each 10 units increase; *** for each 30 min/day increase.

Although the prevalence of AT/AF is significant during the blanking period, with various studies identifying >50 % of the patients having an early recurrence, depending on the type of rhythm monitoring used, a good proportion of patients will still be free of AF at prolonged follow-up [6,16,17]. However, it has been shown that late recurrence is

more frequent in patients who experience AT/AF during the blanking period [20]. Therefore, patients without atrial arrhythmias during the conventional 3-month blanking period are more likely to be AF-free at long-term follow-up.

Previous studies have utilized a wide range of durations for the blanking period post-ablation, making it difficult to define the optimal duration of this particular evaluation period. Also, the degree of arrhythmia burden that better predicts longer-term success has not been quantified.

In our study, we decided to analyze the predictive value of AT/AF occurrence during the “late” blanking period after the ablation procedure (between the 31st and the 90th day) and to assess the best cut-off point for the AT/AF burden regarding the prediction of late AF recurrence. The overall prevalence of AF recurrence was 37,1 % during a long-term follow-up, with a good performance of binary AF burden during the blanking period as a diagnostic test of AF recurrence. An arrhythmia burden > 23 min/day had a negative predictive value of 91,3 % and a positive predictive value of 40,6 % in the prediction of late AF recurrence.

It is important to highlight that close monitoring for recurrence during the blanking period is uncommon [21], which may make our study particularly interesting since we carried out prospectively and systematically an external loop recording in a significant percentage of our patient population.

4.2. Mechanisms of early atrial arrhythmias during the blanking period

The underlying pathophysiological processes responsible for early AT/AF recurrence are not entirely known. Several explanations [22] have been suggested to cause arrhythmias in the early phase after AF ablation. Transient factors [23,24,25], like inflammation, autonomic imbalance, lesions formation, or more extensive ablations, may contribute to the frequent occurrence of AT/AF in the early period post-AF ablation. Arrhythmogenesis during the blanking period seems to be a dynamic process. To avoid the acute effects of energy delivery to the atrial tissue, we included patients studied with the long-duration external monitoring after the first 30 days following the ablation procedure.

4.3. Predictive value of early atrial arrhythmias recurrence

The event external loop recorder is an easily accessible complimentary exam suitable for performing during the blanking period. Our study showed a 25,2 % incidence of AT/AF while monitoring cardiac rhythm during the late blanking period. Overall, these patients had approximately a 4-fold higher risk of late recurrence. The originality of our work is that the cut-off interval of 23 min per day significantly increased the incidence of AF recurrence, with patients showing almost a 7-fold chance compared to those without early AT/AF detection.

In our analysis, not only freedom from early recurrence is a guide to anticipating outcomes, but also the total burden of atrial arrhythmias is an important parameter to be acknowledged.

Therefore, the regular use of long-duration monitoring with an external loop recorder can be beneficial, as it allows the assessment of a simple parameter for evaluating the risk of AF recurrence. The early occurrence of AF above the referred cut-off burden can be seen as a red flag that can eventually justify a more intensive follow-up, maintenance of AAD, and decide chronic anticoagulation (combined with the CHADs-VASc score) or ultimately consider undergoing a re-ablation procedure.

5. Limitations

This study had several limitations. First, this study was designed as a single-center prospective study; thus, it is necessary to validate the results from a prospective study with larger sample size. Secondly, we used standard noninvasive follow-up methods, not invasive methods (e.g., an

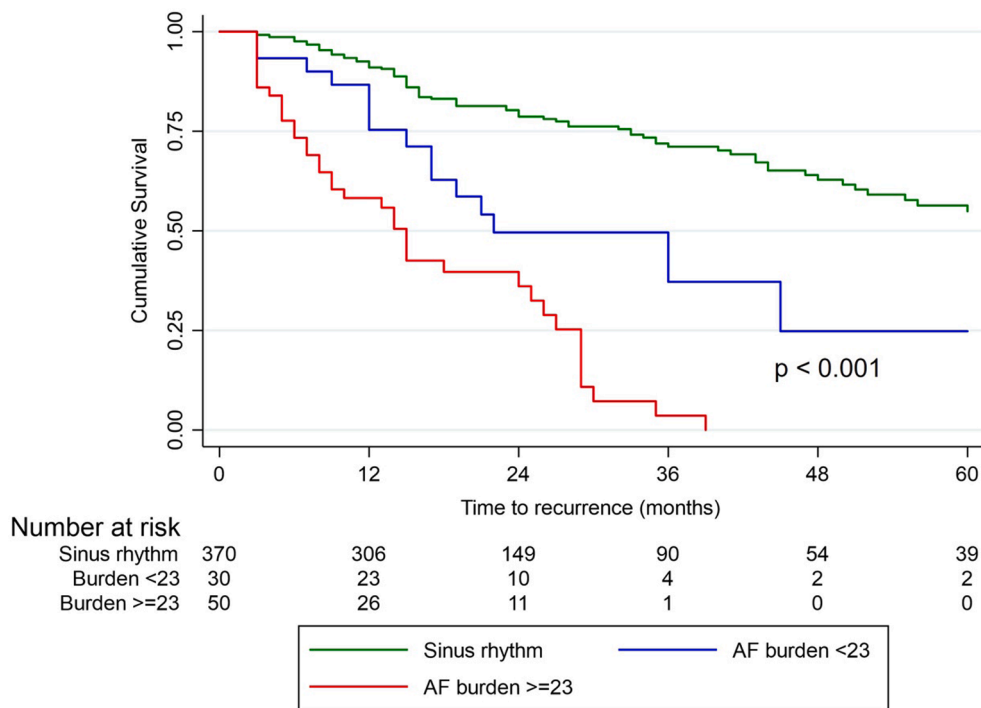


Fig. 4. Kaplan-Meier estimates of recurrence-free survival according to AF burden recorded during the blanking period: sinus rhythm (green line), AF with a mean duration time < 23 min per day (blue line), and AF with a mean duration time ≥ 23 min per day (red line). Twenty-seven patients with AF had missing values in AF burden. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 4
Multivariable analysis results.

Variables	HR estimate	95 % CI	p-value
AF burden*			
AF burden < 23 min/day			
AF burden ≥ 23 min/day	2.60	1.54–4.47	<0.001
AF burden**			
No AF burden (sinus rhythm)	6.79	4.56–10.10	<0.001
AF burden < 23 min/day	0.15	0.10–0.22	<0.001
	0.39	0.21–0.70	0.002
Comorbidities***			
≥ 2 for follow-up time < ≈30 months			
≥ 2 for follow-up time ≥ ≈30 months	1.31	0.91–1.90	0.147
	3.25	1.70–6.23	<0.001

Legend: AF- atrial fibrillation; HR – Hazard Ratio, CI – Confidence Interval; * Reference category: no AF burden (sinus rhythm); ** Reference category: AF burden ≥ 23 min/day; *** Reference category: Zero or one comorbidities.

insertable cardiac monitor). Therefore, detecting AF recurrences after catheter ablation, outside the recording period, particularly in cases with asymptomatic AF, is difficult, and the study might underestimate the recurrence rate.

Thirdly, anti-arrhythmic drugs were continued during the blanking period, which is an important confounder.

A fourth limitation concerns the low number of patients used to obtain the cut-off point for AF burden during the blanking period.

6. Conclusions

The probability of experiencing late recurrence after PVI can be predicted by atrial arrhythmias during the blanking period, with a

higher likelihood if the burden is > 23 min. The blanking period AF burden after PVI should be investigated in future studies.

7. Grant support

This work did not receive any grants or funding.

8. Ethical disclosures

Protection of human and animal subjects. The authors declare that there were no experiments performed on humans or animals for this study.

Registration number and Hospital Ethics Committee approval: number 974/2020.

9. Confidentiality of data

The authors declare that they followed their hospital center’s protocols on the patient data publication.

10. Right to privacy and informed consent

The authors declare that no patient data appear in this article.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijcha.2022.101138>.

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